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Mixed Infection of *Plasmodium malariae* and *Plasmodium falciparum*: A Case Report

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Introduction: Malaria is the most important parasitic infection, which is now spread all over the globe. Malaria infections with more than two species, especially *Plasmodium falciparum* and *P. vivax*, are common, but infections with *P. malariae* and *P. falciparum* are rare.
Case Presentation: A 33-year-old man presented with fever and chills for three days, pancytopenia, and abnormal liver function tests, Peripheral blood smear revealed *P. falciparum* and *P. malariae*. After artemisinin-based combination therapy, all of his symptoms subsided.
Discussion: Mixed malaria infection is not uncommon, and it needs to be diagnosed and treated effectively in order to control the disease. Travel consultations should be given for all travelers before their trip to endemic countries.

Keywords: Malaria; *Falciparum malaria*; *Malariae malaria*; *Plasmodium malariae*; *Plasmodium falciparum*

1. Introduction

Malaria is a vector-born infection caused by *Plasmodium* species, which is transmitted through Anopheles mosquitoes, and it accounts for the majority of cases of illness and fever among travelers (1). Malaria is considered to be a worldwide problem, and it is caused by five different *Plasmodium* spp., *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and the new species *P. knowlesi*. With proper treatment, malaria can be controlled and steps taken to eradicate this infection. In Iran, the major species is *P. vivax* (90%) (2), while the vast majority of malarial cases on the Ivory Coast are due to *P. falciparum* (3), however, cases of *P. malariae* infection mixed with *P. falciparum* are very rare (4). We treated a patient coinfected with *P. malariae* and *P. falciparum*, as discussed below.

2. Case Presentation

A 33-year-old man, who had previously been healthy, was admitted in infectious diseases ward due to fever and chills for three days. The problem started a few days after returning from a 20-day trip to the Ivory Coast, the fever was persistent and had no pattern; the patient denied any animal contact, immunocompromised status, or taking any kind of prescribed or illicit drug. The fever had been between 40-41 °C in the previous three days, without any improvement, even after taking antipyretics, two days later he developed generalized pain with chills. The patient was tachycardic with a pulse rate of 118 bpm and febrile with an oral temperature of 39.9 °C, blood pressure of 135/85 mmHg, and respiratory rate of 20/min. On physical examination, the patient appeared ill and had pale conjunctivae, there was tender and mobile left axillary lymphadenopathy (LAP) 1 × 1 cm and 0.5 × 1.5 cm, and left inguinal 0.5 × 2 cm. Skin findings were normal and there was no sign of bleeding. The patient had pancytopenia and abnormal liver function tests (LFT) (laboratory results can be seen in Table 1). After performing a peripheral blood smear (PBS) the sample was shown to be positive for both *P. falciparum* and *P. malariae* (Figures 1 and 2). The patient was treated with doxycycline 100 mg/BD and artesunate intravenously, with a dose of 2.4 mg/kg at 0, 12, and 24 hours, then subsequently daily. The treatment was continued for seven days, and after excluding Glucose-6-Phophate Dehydrogenase (G6PD) deficiency, primaquine was administrated on the third day at 30 mg/day for the next three days in order to eradicate the gametocytes. PBS was checked at 3, 7, 14, and 28 days, and the results were negative after the seventh day of treatment. Following the seven days of treatment, the patient's symptoms had resolved, including the pancytopenia and abnormal LFT.

Implication for health policy/practice/research/medical education:
This study could help to determine the risk factors for a mixed malaria infection, the countries where it is possible to contract a mixed malaria infection, and the risks of an undiagnosed or subtherapeutic treatment of a mixed malaria infection. Moreover, coinfections should be considered in any patient with a fever who has returned from an endemic country, and to keep this infection in mind during travel consultations before traveling to endemic countries.

Table 1. Complete Blood Count, Biochemistry, and Liver Function[a]

Variables	Data
WBC, μL	2 400
Hb, dL	10.2
Platelets, μL	45 000
AST, U/L	104
ALT, U/L	139
ALP, U/L	178
Bilirubin [T: D], mg/dL	2.3:0.5
LDH, U/L	617
PT, sec	14.6
PTT, sec	28
INR, ISI	1.4
Albumin, g/dL	2.1
K, mEq/L	4.1
Na, mEq/L	135
BUN, mg/dL	17
Cr, mg/dL	0.9

[a] Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine ; Hb, hemoglobin; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothromibin time; PTT, partial thromboplastin time ;WBC, white blood cells

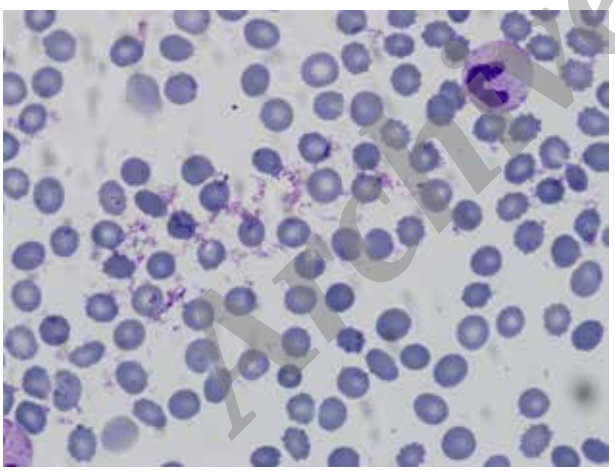

Figure 1. Peripheral Blood Smear With *Plasmodium malariae* and *Plasmodium falciparum*.

3. Discussion

Malaria is considered to be one of the most important parasitic infections throughout the world, and it results in high mortality rates. *Plasmodium* spp. are transmitted by Anopheles mosquitoes. There are four species responsible for malaria, with a newly discovered fifth species known as *P. knowlesi*. The species are: *P. falciparum*, and *P. vivax* which has the widest distribution, (5) *P. ovale* which has been described in the western tropical regions of Africa, *P. malariae* which has a very low prevalence, (6) and the new species *P. knowlesi* which was recognized in 2004, although it had been described previously in 1965, this species is a monkey malaria which is common in Southeast Asia, especially in Malaysia (7).

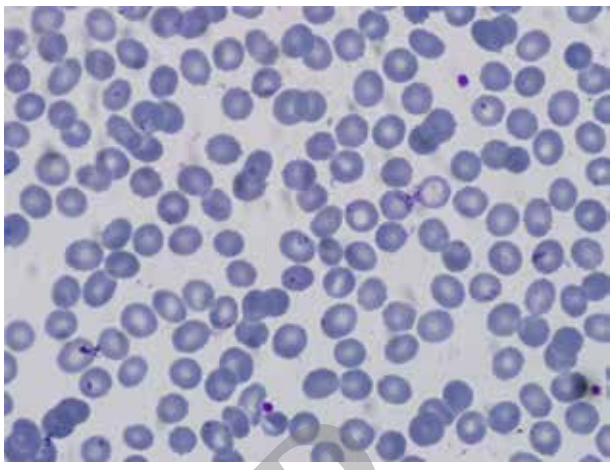

Figure 2. Plasmodium *falciparum* and Plasmodium *malariae* seen in a peripheral blood smear.

The symptoms of malaria vary, but it generally starts as lethargy, anorexia, nausea and vomiting with a headache, accompanied by recurrent intermittent fever and chills with sweating (8). *P. falciparum* can cause both uncomplicated and complicated malaria, which include; respiratory distress or acute respiratory distress syndrome (ARDS), vascular collapse, liver failure, coagulopathy, severe anemia, hypoglycemia, metabolic acidosis, renal failure, and cerebral malaria (9). The other species frequently cause febrile disease; however, this can sometimes be fatal. *P. malariae* can sometimes be asymptomatic, while in other cases it can cause renal failure (10).

Mixed infection of *P. falciparum* and *P. vivax* is not uncommon (11), but *P. falciparum* with *P. malariae* is rare (4, 12). Due to the widespread distribution of *P. falciparum* and *P. vivax*, malaria mixed species infections, which are also defined as coinfections, are the most common causes. These coinfections, even with the right diagnosis, can result in a recurrence after treatment (13).

Plasmodium spp. are diagnosed based on microscopic features of a PBS (14). With mixed-infection cases, it is crucial that the right diagnosis is made in order to determine the most appropriate treatment (15). However, in mixed infections making a diagnosis based on a PBS microscopic diagnosis is challenging, and this can be due to low levels of parasitemia, altered morphology of the parasite due to self-treatment, the similarity in *Plasmodium* spp. e.g. *P. knowlesi* is often misdiagnosed as *P. malariae* or *P. falciparum* (16), but using Polymerase Chain Reaction (PCR) is an effective method in the diagnosis of mixed malaria (17).

One of the main controls for malaria is successful treatment, as under-treatment can lead to the development of resistance and recrudescence (18). *Plasmodium* spp. have developed resistance against older malaria drugs such as chloroquine, and as a result artemisinin-based combination therapies (ACT) have become the first line of treatment for *P. falciparum* and mixed malaria infections. This regimen consists of doxycycline 100 mg/BD and artesunate 2.4 mg/kg, delivered intravenously at 0, 12, and 24 hours, then switching to daily for seven days, and the addition of primaquine 30 mg/day on the third day, for a period of three days, in order to eradicate the gametocytes (19, 20).

Mixed malaria infections are not uncommon, and it is important that they are diagnosed and treated appropriately, in order to control the disease. We recommend that travel consultations should be given to all travelers before their departure to endemic countries.

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Authors' Contributions

Design of the study, scientific collection of information, drafting the paper, reviewing and approving the final version: Mohammad Yasin, Davood Yadegarynia, Amirhossein Moghhtader Mojdehi. Malaria treatment and peripheral blood smear reading: Mahmood Nabavi.

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